UNITED STATES DEPARTMENT OF COMMERCE
**Patent and Trademark Office**
ASSISTANT SECRETARY AND COMMISSIONER OF
PATENTS AND TRADEMARKS
Washington, D.C. 20231

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 23

Serial Number: 08/270152
Filing Date: 7/1/94
Appellant(s): Boussiotis and Nadler

Amy Mandragouras
For Appellant

# EXAMINER'S ANSWER

This is in response to appellant's Brief on Appeal filed 12/22/97.

The text of those sections of Title 35 U.S.Code not included in this appeal can be found in a previous Office action herein.

Appellant's Petition Under 37 CFR 1.181, filed 12/15/97 (Paper No. 31) is acknowledged. Upon reconsideration and in the interest of compact prosecution, appellant's amendment, filed 6/2/97 (Paper No. 25), adding claims 62-67, has been entered.

## (1) Real Party of Interest.

A statement identifying the real party of interest in contained in the Brief.

## (2) Related Appeals and Interferences Identified.

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the Brief.

## (3) Status of Claims.

The statement of the status of claims contained in the Brief is correct.

This Appeal involves claims 48, 50-61 and 97-98.

(4) **Status of Amendments After Final.**

The appellant's statement of the status of amendments after final rejection contained in the Brief is correct.

Appellant's amendment, filed 12/22/97 (Paper No. 21), with the Appeal Brief (Paper No. 22), is acknowledged and has been entered. The cancellation of claims 49, 51-54, 62-96 and 99-101 and the amendment of claims 48, 50, 55-56 and 98 have reduced the number of issues for appeal.

Appellant Petition under 37 CFR 1.181 To Withdraw Finality of Rejection, filed 12/22/97 (Paper No. 21), is acknowledged. Appellant's arguments have been fully considered but are not found convincing. Appellant's arguments appear to indicate to that the first ground or rejection under 35 USC 112, first paragraph, was drawn to enablement of clinical applications of the claimed methods, while the second ground of rejection was based on the predictability of success of the in vitro and in vivo therapeutic methods encompassed by the instant claims. In contrast to appellant's assertions of different grounds of rejection and the deprivation of an opportunity to respond; the rejection of record under 35 USC 112, first paragraph, have addressed the predictability of the claimed methods based on the instant disclosure as they apply to enablement and scope issues under the Forman Factors. Appellant's arguments are not found persuasive.

(5) **Summary of Invention.**

The summary of invention contained in the Brief is correct.

(6) **Issues.**

The appellant's statement of the issues in the Brief is incorrect.

In view of the entry of appellant's amendment, filed 12/22/97 (Paper No. 21), which canceled claims 49, 51-54, 62-96 and 99-101 and amended claims 48, 50, 55-56 and 98; the remaining issue is whether claims 48, 50, 55-61, 98 are adequately described and enabled under 35 USC 112, first paragraph.

Upon reconsideration of appellant's amended claims, claim 97 is allowable. Therefore, claim 97 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The previous rejections under 35 USC 112, second paragraph, and 102 (a)(b)(e) are rendered moot in view of appellant's amendment, filed 12/22/97 (Paper No. 21).

(7) **Grouping of Claims.**

The appellant's statement in the Brief the certain claims do not stand or fall together is not agreed with because of the entry of appellant's amendment, filed 12/22/97 (Paper No. 21), which canceled claims 49, 51-54, 62-96 and 99-101 and amended claims 48, 50, 55-61 and 98. The rejection of claims 48, 50, 55-61 and 98 stand or fall together because the sole issue under appeal is the rejection under 35 USC 112, first paragraph, as it relates to stimulating T cell responsiveness in T cells or anergic T cells with anti-γ chain antibody. However, it is noted that the 112, first paragraph, rejection is maintained with respect to in vivo methods of stimulating T cells (claims 48, 50, 55-61 and 98) and with respect to both in vitro and in vivo methods of stimulating anergic T cells (claim 98).

As indicated above in Issues, the previous rejections under 35 USC 112, second paragraph, and 102 (a)(b)(e) are rendered moot in view of appellant's amendment, filed 12/22/97 (Paper No. 21).

Also, as set forth above in Issues, claim 97 is considered allowable and is objected to and not rejected.

(8) **Claims Appealed.**

The copy of the appealed claims contained in the Appendix to the Brief is correct.

(9) **Art of Record.**

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

A) Basker et al., PNAS 90: 5687-5690 (1993).
B) Boussiotis et al. Science, 266: 1039-1042 (1994)
C) Boussiotis et al. Research in Immunology 146: 140-149 (1995).
D) Blue stone Immunity 2: 555-559 (1995).
E) Russell et al., Science, 262: 1880-1883 (1993).

(10) **Grounds of Rejection.**

The following ground(s) of rejection are applicable to the appealed claims.

**Rejection Under 35 U.S.C. § 112, First Paragraph**

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the in vitro experimental conditions accurately reflects the relative efficacy of the claimed therapeutic strategy to stimulate T cell responsiveness with cytokine receptor γ chain-specific antibodies (claims 48, 50, 55-61), including stimulating responsiveness in anergic T cells (claim 98). It is noted that prior to appellant's amendment, filed 12/22/97 (Paper No. 21), with the Appeal Brief (Paper No. 22); the pending claims were drawn to modulating or inhibiting T cell unresponsiveness, such that T cell stimulation occurs.

Pharmaceutical therapies are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Appellant provides data wherein the addition of IL-2, IL-4 or IL-7 to the primary culture of T cell clones prevention the induction of anergy. The experimental data also indicates that cross-linking of γ chain during the primary culture prevented the induction of anergy and resulting in both proliferation and IL-2 secretion during rechallenge. Although this provides some evidence that after T cell receptor signaling, an event mediated through the γ chain prevents the induction of anergic state, this analysis only helps to begin to decipher the molecular mechanisms associated with T cell anergy (Boussiotis et al. Science, 1994; last paragraph).

However, there is insufficient information or nexus of how to use this information in the generation of therapeutic methods to stimulate T cell responsiveness in vivo including stimulating responsiveness in anergic T cells in vitro or in vivo. Appellant's experimental evidence relies upon well defined culture conditions using T cell lines. However, there is insufficient evidence that such an experimental model mimics the in vivo or clinical situation encompassed by the claimed methods; therefore, the predictive value of such an in vitro model remains unknown.

Russell et al. (Science, 1993) addresses the complexity of controlling targeting gamma systems (see entire document, particularly page 1882, column 3, paragraph 1). Certain activation events, such as B7 expression on B cells and T cell proliferation, can be induced by IL-2 or IL-4. Conversely, IL-4 inhibits IL-2 binding to some cell lines and IL-2 mediated growth. Depending on the amount used, IL-4 can either augment or inhibit IL-2 mediated generation of natural killer cells. These findings may be explained by the differential recruitment of $\gamma_c$ into one system and its concomitant sequestration from the other.

Boussiotis et al. (Research in Immunology, 1995) discloses that CD28 costimulation can prevent but cannot reverse anergy (see entire document, particularly pages 144-146).

Blue stone et al. (Immunity, 1995)reviews the complexity of in vitro and in vivo models of T cell costimulation (see entire document, particularly page 558, column 2, paragraph 2).

Therefore the art recognizes that signaling via costimulatory pathways is complicated and is very dependent on various parameters, such as cross-linking, the nature and state of T cell activation, the nature and density of targeted antigen on said T cells, and the nature of the agent.

It is noted that in stimulating T cells via costimulatory molecules, the administration of such a signal via cytokine receptor γ chain-specific antibodies is compromised by the half-life of such signaling and the need to obtain the signaling in quantities sufficient to achieve effective dose levels. The disclosed experimental evidence requires cross-linking of γ chain-specific antibodies to stimulate T cells (Example 2). However, there is a lack of direction and objective evidence that one could provide sufficient cross-linking at an appropriate time point in vivo to stimulate T cell responsiveness. Also, as pointed out above, anergic T cells appear refractory to stimulation via costimulatory molecules. Therefore, the specification does not teach how to extrapolate data obtained from in vitro assays of cross-linking T cell lines with γ chain-specific antibodies to the development of effective in vivo human therapeutic methods, commensurate in scope with the claimed invention.

There is insufficient evidence that the available in vitro or vivo data would predict a systemic stimulation of T cell responsiveness to the scope of antigens encompassed by the claimed methods, including tumors, viruses, bacteria and parasites by administering cytokine receptor γ chain-specific antibodies. With respect to either stimulating T cell responsiveness associated with tumors, pathogens, bacteria and viruses (claims 48, 50, 56-61) or with respect to stimulating responsiveness in anergic T cells (claim 98); the claimed methods encompass conditions which are diagnosed and treated after tumor or infectious agents are already in place or cells that are already anergic. For example, tumors comprise self antigens that would not be recognize as foreign; therefore the subject would likely be anergic, at least to some degree, to such tumor or self antigens occur long before the administration of cytokine receptor γ chain-specific antibodies to stimulate T cell responsiveness in therapeutic methods, encompassed by the claimed methods.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective pathogen- and tumor- based therapies relying upon cytokine signaling, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for stimulating T cell responsiveness in T cells in vivo or anergic T cells in vitro or in vivo.

**(11) Response to Argument**

**Rejection Under 35 U.S.C. § 112, First Paragraph**

Appellant's arguments have been fully considered but are not found convincing.

Appellant submit that the rejection of record does not apply to the claims as amended.

It is noted that appellant indicates that all of the remaining claims depend from claim 48, however claim 98 is an independent claim and is drawn to stimulating responsiveness in an anergic T cell (versus a T cell which expresses a cytokine receptor γ receptor).

Appellant reiterate their arguments that the relevant question is whether the specification "adequately teaches one of ordinary skill in the art how to make and use the claimed invention" and that the proper standard for judging enablement of claims involving an asserted therapeutic effect is whether the disclosure provides sufficient guidance and data which would lead one of ordinary skill in the art to reasonably believe the asserted utility of effect (In re Brana, 34 USPQ2d 1437 (CAFC 1995)). Appellant argues that further evidence should not be required to satisfy the enablement requirement of section 112, first paragraph, unless there is reason to doubt the objective truth of the asserted utility. Appellant maintains that the disclosure fully satisfies this enablement standard.

Appellant argues that page 18, line 16 through page 20, lines 19 of the instant specification describes methods for administering agents such as anti-γ chain antibodies to stimulate T cell responses.

Appellant argues that Examples 1 and 2 on pages 21 and 23 of the instant specification provides working examples demonstrating that agents within the scope of appellant's claims prevent the induction of T cells anergy in a human alloantigen specific T cell clonal model system. Appellant asserts that the data presented in the specification is more than reasonably indicative of in vivo efficacy as asserted and claimed by appellants and that human T cells and cell lines are routinely used to illustrate immune system responses in vitro and art accepted models of in vivo therapeutic efficacy.

While human T cells and cell lines are routinely used to illustrate immune system responses in vitro, such in vitro systems are not art accepted models of in vivo therapeutic efficacy.

Again, appellant is reminded of the factors to be considered in determining scope and enablement ; 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986. As the breadth and the intention of the claimed methods do read on normal or primed T cells either ex vivo as well as in vivo. Although appellant relies upon the specification to discloses how to make and to use the claimed methods, there is insufficient objective evidence to support the breadth and the predictability of stimulating T cells responsiveness in T cells in vivo or anergic T cell in vitro or in vivo, for the reasons of record and indicated above in section 10. The issue involved is whether or not the evidence of record was based on in vitro studies is generally recognized by those of ordinary skill in the art as being reasonably predictive of success in the practical in vitro and in vivo therapeutic methods encompassed by the instant claimed methods.

Appellant relies upon the holding and dicta in In re Brana 34 USPQ2d 1436 (Fed. Cir. 1995) that their position that it is not necessary to supply in vivo clinical data to support claims of the type proposed here. However, Brana was directed to chemical chemotherapeutic compounds structurally similar to other compounds known in the art and for which animal models were art recognized to be predictive of the therapeutic usefulness and which were, as a class, recognized to be effective in treating tumors . The examiner agrees that the it is unnecessary that appellant must prove the ultimate value in humans of their asserted utility. The issue in this case is not whether the general description in the specification of utility, practical or otherwise, for a claimed compound reasonably satisfies the utility requirements of 35 U.S.C. 112, first paragraph and 101, as the Court viewed the case in Brana. Rather the issue here is that appellant's specification provides insufficient information or nexus which enables any person skilled in the art to use the full scope of the broadly claimed therapeutic methods to stimulate the responsiveness of T cells in vivo or to stimulate the responsiveness of anergic T cells in vitro or in vivo with anti-γ chain antibodies.

As set forth in previous Office Actions (Paper Nos. 11, 15, 18) and reiterated above in section 10; the examiner has set forth both scientific reasoning and evidence as to the unpredictability of stimulating T cells and anergic T cells via costimulatory molecules, including targeting the γ chain with anti-γ chain antibodies.

Appellant's stimulation of T cells with anti-γ chain antibodies requires cross-linking (e.g. via rabbit anti-mouse Ig) in the presence of T cell receptor signaling (see Example 2 on page 23 of the specification). The specification does not provide sufficient information how to achieve such cross-linking in vivo. It is noted that page 16, paragraph 3 of the instant specification discloses that anti-γ chain antibodies can serve to stimulate signaling via the cytokine receptor gamma chain, provided that the antibody is crosslinked either by secondary antibodies or bound to a solid support (see Anti-γ chain Antibodies). Alternatively, it is noted that page 13, paragraph 1 of the instant specification discloses that anti-γ chain antibodies can serve to inhibit signaling via the cytokine receptor gamma chain, provided that do not crosslink gamma chain (see Anti-γ chain Antibodies). Therefore, in the absence of cross-linking, the same anti-γ chain antibodies appear to inhibit signaling via the γ chain receptor.

With respect to anergic cells (claim 98), the evidence of record as indicated above in section 10, including the co-inventors' own work indicates that such anergic cells are refractory to stimulation via costimulation (see Boussiotis et al., Research in Immunology, 1995; particularly pages 144-146). Appellant's disclosed Examples rely upon T cells and not anergic T cells. Further appellant has not provide objective evidence to support the ability of stimulating anergic T cell responsiveness either in vitro or in vivo.

Therefore, for the reasons of record and set forth above, appellant's arguments are not found persuasive and the rejection is maintained.

**(12)** For the above reasons, it is believed that the rejections should be sustained.

Respectively submitted,

Lila Feisee
Supervisory Primary Examiner

Phillip Gambel
Patent Examiner
Technology Center 1600
March 16, 1998